Optimizing Risk Stratification in Acute Myeloid Leukemia: Dynamic Models for a Dynamic Therapeutic Landscape

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Acute myeloid leukemia (AML) is a heterogeneous disorder in which clinical outcomes are determined predominantly by patient age, karyotype, and genomic features.[1] Historically, much of this information has had little impact on treatment decisions for AML as the standard treatments were largely limited to intensive chemotherapy, with or without allogeneic hematopoietic stem-cell transplantation (HSCT), for fit patients and low-dose cytarabine or supportive care for older, unfit patients (with more recent options of azacitidine or decitabine monotherapy available off-label for AML in the United States in 2004 and 2006, respectively). However, in the past 5 years our knowledge of the molecular features that drive outcomes in AML has increased exponentially, in parallel with an unprecedented expansion of therapeutic options for this disease.[2] In this rapidly evolving landscape, it is vital that our risk assessment tools and resultant therapeutic guidelines are equally dynamic. In this commentary, we discuss the limitations of our current risk stratification guidelines in AML and propose improvements that will more accurately reflect the best available evidence and inform optimal therapy.

At present, the most widely used consensus risk stratification guidelines in AML—those from the European LeukemiaNet (ELN) and from the National Comprehensive Care Network (NCCN)—are based exclusively on cytogenetic or molecular features. In 2010 the ELN, an international working group of 19 AML experts, proposed to standardize reporting in clinical trials on the basis of karyotype and the presence or absence of *CEBPA*, *FLT3*, or *NPM1* mutations.[3] In addition to harmonizing clinical trial reporting, these classifications were also used to recommend specific postremission therapies. For example, patients with favorable-risk disease were recommended to receive chemotherapy consolidation alone, whereas those with adverse-risk disease were recommended consolidative HSCT. All these recommendations are category 2A, reflecting low-level evidence but with uniform panel consensus. In the most recent ELN consensus document from 2017, the risk categories were updated to incorporate emerging data about other disease-modifying genomic alterations, including *RUNX1*, *ASXL1*, and *TP53* mutations, as well as the prognostic importance of *FLT3* internal tandem duplication allelic ratio.[4] Although the NCCN had initially developed its own risk groups (initially on the basis of cytogenetics alone and later incorporating frequently recurring molecular mutations) that differed somewhat from that of the ELN, the proposals of the ELN and NCCN are now identical, and thus, in effect only one widely used method of risk stratification in AML presently exists in the United States and Europe.[5]

There is certainly some utility in a uniform consensus on expected relapse risk and survival among defined groups that allows for comparison across retrospective and prospective clinical studies in AML. However, there are several deficits with the present system that limit its wide applicability in the modern era. It is notable that these risk groups were developed on the basis of data sets almost exclusively consisting of younger, fit patients with de novo AML treated with intensive chemotherapy (generally 7 + 3 or similar chemotherapy, followed by high-dose cytarabine consolidation). However, AML is largely a disease of older age, with a median age at diagnosis of 68 years.[1] It has been estimated that approximately 80% of patients age ≥ 65 years are predicted to have induction mortality rates of ≥ 30% with intensive chemotherapy.[6] Perhaps in part because of concerns about unacceptable treatment-related mortality with intensive chemotherapy, recent studies suggest that the majority of patients with newly diagnosed AML who are age > 60 years receive lower-intensity therapies.[7] The share of older adults receiving lower-intensity therapy is likely to further increase as we now have highly effective venetoclax-based therapies that are associated with significantly lower rates of early mortality and better overall survival (OS) in these older patients, as compared with intensive chemotherapy.[8] In light of the current practice patterns that favor lower-intensity therapies for most older adults, the present risk stratification guidelines and recommendations for postremission therapies may actually only apply to a

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minority of patients with newly diagnosed AML, significantly limiting the generalizability of these guidelines.

Our current methods of risk stratification also fail to account for the most significant patient-related and other clinical factors that influence prognosis, thus making meaningful comparisons across some groups particularly challenging and leading to relative rather than absolute risk groups. This is particularly notable for older adults with AML. Two recent validation studies of the ELN 2017 risk stratification in patients ≥ 60 years treated with intensive chemotherapy confirmed that this classification was able to divide patients into three distinct risk groups.[9,10] However, the outcomes even for so-called favorable-risk older adults are poor. In one analysis of older patients with AML, the 3-year OS rates for favorable-, intermediate-, and adverse-risk groups were 30%, 12%, and 6%, respectively.[9] Thus, older patients with favorable-risk AML by our current classifications have outcomes that approximate those of adverse-risk disease in younger patients. This discrepancy in outcomes highlights that classification of patients as having favorable-, intermediate-, or adverse-risk disease is largely meaningless without knowledge of relevant patient-related factors, particularly age. Not surprisingly, when age is considered in our risk assessment, our ability to predict OS is substantially improved, particularly in older adults.[11] Relevant comorbidities, which often correlate with patient age but may also be independent of age, can be captured by a number of different risk assessment tools.[12] Consideration of these comorbidities, although often complex to quantify in clinical practice, may nonetheless refine our prognostication and also inform assessment of an individual patient's suitability for consolidative HSCT.

Although age is certainly one of the most powerful factors that influences long-term OS in AML, it is important to consider other well-established clinical variables when risk stratifying patients. Even in the most comprehensive analyses of cytogenetic and molecular risk factors in AML, it has been estimated that these genetic factors account for up to 60%-70% of OS estimates, with the rest explained by demographic characteristics, clinical variables, or differing treatments.[13] However, at present, patient-related or clinical characteristics are not included in the widely used ELN and NCCN risk stratification guidelines. As the data supporting the current cytogenetically and molecularly defined risk groups are derived predominantly from younger patients with de novo AML, clinically relevant historical factors such as preceding myelodysplastic syndrome (MDS) or myeloproliferative neoplasm (secondary AML) or prior exposure to cytotoxic chemotherapy or irradiation (therapy-related AML) are not considered, despite the worse outcomes observed with these entities.[14-17] Patients with secondary AML who received prior treatment for an antecedent hematologic malignancy (eg, a hypomethylating agent [HMA] for MDS) have particularly dismal outcomes even in the absence of adverse-risk cytomolecular features, with a median OS < 6 months.[15] Yet, this relevant clinical history is not considered in our current risk stratification guidelines. Even in patients with core-binding factor AML, which is currently defined as a favorable-risk subtype of AML, those with therapy-related disease have dismal outcomes with a 5-year OS < 20%, highlighting the importance of considering relevant clinical factors in risk assessment.[18]

In the setting of new effective drugs and combination regimens, it is also vital to ensure that our risk stratification systems remain relevant within the current treatment paradigm. The standard of care for frontline AML therapy is rapidly evolving, and thus, many prognostic factors derived from an era of 7 + 3 for nearly all patients may become irrelevant. For example, the addition of FLT3 inhibitors into frontline regimens may overcome the historically poor prognosis associated with *FLT3* internal tandem duplication–mutated AML, including cases with high allelic ratios, where a long-term OS > 50% has been achieved in some studies.[19,20] For older adults with newly diagnosed AML who are unfit for intensive chemotherapy, the combination of an HMA (eg, azacitidine) plus venetoclax is a new standard of care that is widely used in both community and academic practice. It is therefore important to understand the cytogenetic and/or molecular features that may uniquely predict for clinical outcomes in patients treated with this regimen.[21] Although multiple previous analyses have suggested that *IDH1* or *IDH2* mutations do not strongly influence OS in the context of conventional chemotherapy regimens, venetoclax-based therapies are highly effective in *IDH*-mutated AML, with a median duration of response not reached and a median OS > 24 months reported in older adults treated with an HMA plus venetoclax.[22] Similarly, in a retrospective analysis of patients with *NPM1*-mutated AML treated with intensive chemotherapy, an HMA alone, or an HMA plus venetoclax, treatment with the HMA plus venetoclax regimen (but not ELN 2017 risk group) emerged as a predictor for OS.[23] These examples highlight the interplay between the type of treatment and clinical outcomes.

Risk stratification for complex diseases such as AML will always be imperfect, and no system is likely to account for the many intricate interactions between all patient-related, disease-related, and treatment-related variables. However, there is still much room for improvement with the current consensus approach to risk assessment in AML as published by both the ELN and NCCN. We therefore propose two broad principles that can be used to refine our current guidelines. First, prognostic groups should be defined on the basis of absolute rather than relative OS estimates. This will eliminate the counterintuitive conclusions that many favorable-risk patients (according to current guidelines) might actually have expected long-term OS rates < 20%. One potential proposal to address this issue is to define risk groups on the basis of expected 3-year OS rates, for example, categorizing patients into favorable-, intermediate-,

and poor-risk groups with 3-year OS rates of > 60%, 30%-60%, and < 30%, respectively. Alternatively, other systems that further divide patients into prognostic subgroups with increased discrimination for clinical outcomes (eg, into five or more groups, similar to the Revised International Prognostic Score Systems for MDS) could be considered. Such a classification would necessitate considering the most relevant clinical features that influence OS, particularly patient age, thus creating a risk stratification system that extends beyond cytomolecular features alone. How to optimally incorporate the major clinical, cytogenetic, and molecular prognostic factors into a more accurate system of risk assessment in AML is a complex undertaking. Undoubtedly, there are a myriad of acceptable ways in which these new classifications could be devised (eg, a categorization similar to the current ELN and NCCN guidelines but that also incorporates relevant clinical features or, alternatively, a scoring system that weighs each prognostic factor and then generates a composite risk score). However, regardless of the specifics, we believe that developing a risk stratification system that more accurately reflects an individual patient's expected survival outcomes would be a great improvement both for AML research (thereby facilitating more accurate comparisons across published data of heterogeneous populations) and for routine clinical care. Although one strength of the current ELN and NCCN guidelines is their relevance to the selection of postremission therapies for younger, fit, and transplant-eligible patients with de novo AML, because it does not take relevant clinical features into account, this system fails to capture many adverse-risk patients. For example, a younger, fit patient who develops AML after prior HMA-based therapy for MDS is expected to have very poor outcomes regardless of cytogenetic or molecular features at the time of AML transformation and should be recommended for HSCT in first remission.[15]

The second guiding principle we propose is that these risk groups must be dynamic as new, more optimal therapies emerge for specific disease subsets. Seven years passed between the last two ELN consensus guideline publications, and nine new drugs have been approved for AML by the FDA since the publication of the last guidelines. By contrast, the NCCN refines their treatment algorithms on the basis of new drug approvals and data at least annually (often more frequently). Thus, the NCCN may be well-positioned to create such an innovative and dynamic model of risk stratification in AML that distinguishes itself from the ELN guidelines, which can be used by clinicians and researchers in the context of the most up-to-date clinical data and contemporary treatments (eg, the routine incorporation of FLT3 inhibitors into frontline AML therapy or the use of low-intensity venetoclax-based regimens in older adults). However, our proposal is not limited to the NCCN. For any new risk stratification guidelines to be widely adopted both nationally and internationally, collaborations among leading groups of academic hematologists and oncologists, including the American Society of Hematology, the WHO, and other groups of international prominence, are imperative. Also, it is important to note that any new risk stratification system need not be in conflict with the current ELN guidelines but rather should be viewed as complementary. Although the AML risk stratification by the ELN provides important guidance for selection of postremission therapies (eg, consolidative chemotherapy versus HSCT) for fit patients with de novo AML treated with conventional cytarabine- and anthracycline-based induction, a more dynamic risk stratification system on the basis of the principles we have outlined herein will provide somewhat different—yet still very clinically valuable—information. Specifically, such a system should ideally provide a more accurate prediction of expected outcomes on the basis of an integrated analysis of clinical, cytogenetic, and molecular factors and in the context of treatment with the best available contemporary therapies. As more effective agents and regimens are developed, including for historically adverse-risk AML subsets (eg, FLT3 inhibitors for newly diagnosed *FLT3*-mutated AML), our calculation of disease risk and also who should or should not undergo HSCT in first remission is likely to shift over time. Optimal risk stratification systems should be able to account for these changes, and to do so, they must be updated frequently on the basis of emerging data and evolving standards of care.

In summary, a dynamic model of risk assessment on the basis of absolute rather than relative OS estimates would not only improve our clinical predictions in individual patients but would also allow for better comparison of data across retrospective and prospective studies, by determining how outcomes of different risk groups compare with expectations with our best available therapies. As a community of AML physicians and researchers, it is time that we reconceptualize our approach to risk stratification for this disease. In assessing an individual patient's risk of relapse and likelihood of long-term survival, we should not simply ignore the most relevant clinical and patient-related factors that have consistently been shown to affect prognosis. Furthermore, we must embrace the notion that novel therapies with novel mechanisms of action will often have novel predictive factors. In this exciting new era of drug development and discovery in AML, dynamic risk models that account for a rapidly evolving therapeutic landscape are now needed more than ever.

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REFERENCES

1. Short NJ, Rytting ME, Cortes JE: Acute myeloid leukaemia. Lancet 392:593-606, 2018
2. DiNardo CD, Perl AE: Advances in patient care through increasingly individualized therapy. Nat Rev Clin Oncol 16:73-74, 2019
3. Döhner H, Estey EH, Amadori S, et al: Diagnosis and management of acute myeloid leukemia in adults: Recommendations from an international expert panel, on behalf of the European LeukemiaNet. Blood 115:453-474, 2010
4. Dohner H, Estey E, Grimwade D, et al: Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 129:424-447, 2017
5. Tallman MS, Wang ES, Altman JK, et al: Acute myeloid leukemia, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw 17: 721-749, 2019
6. Kantarjian H, O'Brien S, Cortes J, et al: Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: Predictive prognostic models for outcome. Cancer 106:1090-1098, 2006
7. Medeiros BC, Pandya BJ, Hadfield A, et al: Treatment patterns in patients with acute myeloid leukemia in the United States: A cross-sectional, real-world survey. Curr Med Res Opin 35:927-935, 2019
8. Maiti A, Qiao W, Sasaki K, et al: Venetoclax with decitabine vs intensive chemotherapy in acute myeloid leukemia: A propensity score matched analysis stratified by risk of treatment-related mortality. Am J Hematol 96:282-291, 2020
9. Eisfeld AK, Kohlschmidt J, Mrózek K, et al: Mutation patterns identify adult patients with de novo acute myeloid leukemia aged 60 years or older who respond favorably to standard chemotherapy: An analysis of Alliance studies. Leukemia 32:1338-1348, 2018
10. Herold T, Rothenberg-Thurley M, Grunwald VV, et al: Validation and refinement of the revised 2017 European LeukemiaNet genetic risk stratification of acute myeloid leukemia. Leukemia 34:3161-3172, 2020
11. Straube J, Ling VY, Hill GR, et al: The impact of age, NPM1(mut), and FLT3(ITD) allelic ratio in patients with acute myeloid leukemia. Blood 131:1148-1153, 2018
12. Cortes JE, Mehta P: Determination of fitness and therapeutic options in older patients with acute myeloid leukemia. Am J Hematol 96:493-507, 2021
13. Papaemmanuil E, Gerstung M, Bullinger L, et al: Genomic classification and prognosis in acute myeloid leukemia. N Engl J Med 374:2209-2221, 2016
14. Granfeldt Ostgard LS, Medeiros BC, Sengelov H, et al: Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: A national population-based cohort study. J Clin Oncol 33:3641-3649, 2015
15. Boddu P, Kantarjian HM, Garcia-Manero G, et al: Treated secondary acute myeloid leukemia: A distinct high-risk subset of AML with adverse prognosis. Blood Adv 1:1312-1323, 2017
16. Samra B, Richard-Carpentier G, Kadia TM, et al: Characteristics and outcomes of patients with therapy-related acute myeloid leukemia with normal karyotype. Blood Cancer J 10:47, 2020
17. Kayser S, Döhner K, Krauter J, et al: The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 117:2137-2145, 2011
18. Borthakur G, Lin E, Jain N, et al: Survival is poorer in patients with secondary core-binding factor acute myelogenous leukemia compared with de novo core-binding factor leukemia. Cancer 115:3217-3221, 2009
19. Yalniz F, Abou Dalle I, Kantarjian H, et al: Prognostic significance of baseline FLT3-ITD mutant allele level in acute myeloid leukemia treated with intensive chemotherapy with/without sorafenib. Am J Hematol 94:984-991, 2019
20. Wei AH, Kennedy GA, Morris KL, et al: Results of a phase 2, randomized, double-blind study of sorafenib versus placebo in combination with intensive chemotherapy in previously untreated patients with FLT3-ITD acute myeloid leukemia (ALLG AMLM16). Blood 136:36-38, 2020 (suppl 1)
21. DiNardo CD, Jonas BA, Pullarkat V, et al: Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med 383:617-629, 2020
22. DiNardo CD, Pratz K, Pullarkat V, et al: Venetoclax combined with decitabine or azacitidine in treatment-naive, elderly patients with acute myeloid leukemia. Blood 133:7-17, 2019
23. Lachowiez CA, Loghavi S, Kadia TM, et al: Outcomes of older patients with NPM1-mutated AML: Current treatments and the promise of venetoclax-based regimens. Blood Adv 4:1311-1320, 2020

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